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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,338	06/18/2001	Sohei Kanno	209861US0PCT	8914

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/868,338	**Applicant(s)** KANNO ET AL.	
	Examiner Nirmal S. Basi	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 January 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): The written description rejection under 35 USC first paragraph.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *7,15 and 16*.
   Claim(s) withdrawn from consideration: *1-4 and 9-14*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

AC

N16.

Continuation of 11. does NOT place the application in condition for allowance because: the claims remian rejected 35 U.S.C. 101 and 35 U.S.C. first paragraph for reasons of record. The asserted utility of the claimed gene and protein of the present invention is that they are useful for breeding of a microorganism for the purpose of modifying transport of amino acids across a cell membrane. The claimed gene and protein are argued to be members of a family of genes/proteins which are known in the art as ATP binding cassette transporters (ABC transporters). Applicant argues the ATP transporters have an established physiological function of uptake and excretion of substances into and out of the cell. This function is argued to be an important and defined function in the cell machinery, allowing a cell to excrete toxic and unneeded substances, while importing useful substances for its metabolism. Applicant argues transporters have a defined and credible usefulness which is practical in that these proteins can be expressed in a cell and effect the transport of substances, and in the instant invention, amino acids, inside and outside of the cell. Applicant further argues any person of ordinary skill in the art would recognize this utility as useful in its currently available form and not merely an object of further use testing Applicants arguments have been fully considered but not found persuasive for the reason given below:

Based on the record, there is not a "well established utility" for claimed ABC transporter because the amino acids transported by claimed invention have not been disclosed. The ABC transporters comprise a family of functionally and pharmacologically diverse compound transporters with diverse effects (see Higgins, IDS ref AAA, previousoffice Action).

Higgins, (page 68 and Table 1), discloses that the designation ABC transporters recognizes a highly conserved ATP-binding cassette, which is the most characteristic feature of this super family. Some ABC transporters require an associated periplasmic receptor for uptake, others do not. Some ABC transporters have a role in multidrug resistance, others do not. Over 50 ABC transporters are known. Typically, ABC transporters utilize the energy of ATP hydrolysis to pump substrates across the membrane against a concentration gradient , but again there are exceptions. Each ABC transporter is relatively specific for a given substrate. ABC transporters are specific for amino acids, sugars, inorganic ions, polysaccharides, peptides, and even proteins have been characterized (Table 1). Some ABC transporters are uptake (import) systems that accumulate substrate within the cell, while others export substrate from the cell, none has been identified that can pump in both directions.

Further, page 78, Higgins discloses, comparison of the amino acid sequences of the transmembrane domains of one transporter with those of another reveals little or no significant similarity (except for a few specific cases). The only significant sequence conservation between the transmembrane domains of several different ABC transporters is a short motif identified on many bacterial transporters. Sequence similarity has been detected between the yeast STE6 peptide transporter and Hlyb hemolysin exporter, and human P-glycoprotein (all transport different compounds)

On page, 86 Higgins discloses, ABC transporters have been identified for almost every class of substrate imaginable, including sugars, peptides, inorganic ions, amino acids, oligopeptides, polysaccharides, and proteins (Table 1). Not only are these substrates chemically very different, but they also vary enormously in size. The mechanism by which such diversity is achieved, while each transporter retains a high degree of selectivity for its own particular substrate, 'presents an intriguing problem. ' .

On page 88, Higgins discloses, even close similarities between ABC transporters can be misleading: the Mal and Ugp transport systems of E. coli are closely related yet handle different substrates and the two human mdr genes are very similar to each other, yet only one is able to mediate drug transport.

The specification does not disclose the compounds transported by claimed transporter. The prior art discloses that the substrate transported cannot be determined based on sequence homology. It is not even clear if claimed invention is an import or an export system. The specifcation, page 9, discloses compounds with sequence homoly to claimed invention (31.0%-35.4%), transport a diverse number of amino acids. Based on the specifcation and prior art it cannot be predicted which compounds are transported by claimed invention and how the manipulation of said transport would be useful in breeding microorganisms. Does the claimed ABC transporter import or export amino acids, sugars, inorganic ions, polysaccharides, peptides or some other compound? Will the export or import of a compound be useful for breeding of a microorganism for the purpose of modifying transport of amino acids across a cell membrane. What compound is transported? What level of transport will be benificial to the organism? There are no examples provided in the specification or prior art where the claimed ABC transporter of SEQ ID NO:9 has been used for the purpose of breeding of a microorganism for the purpose of modifying transport of amino acids across a cell membrane.

Therefore the utilities asserted by Applicant are not specific or substantial. Neither the specification nor the art of record disclose the protein of SEQ ID NO:9 encoded by the DNA of SEQ ID NO:7 or fragments thereof useful for the purpose of breeding of a microorganism for the purpose of modifying transport of amino acids across a cell membrane. There is no disclosure of the beneficial affects of claimed transporter in bacteria which can be utilized for breeding. Thus the corresponding asserted utilities for the ABC transporter, with no disclosed ligands or compounds which it transports, are essentially methods of treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. It would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the ABC protein/DNA and fragments thereof, further experimentation is necessary to attribute a utility to the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535B36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose soleutility consists of its potential role as an object of use testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

The specification discloses the claimed ABC protein/DNA is related to other proteins of the ABC transporter family. Applicant has used the homology to form the basis for utility for the claimed ABC protein/DNA. There is no disclosure in the art that proteins which have the homology disclosed in the specification are sufficiently similar and have the same function or transport the same compounds. Based on the art and Applicants specification that the ABC transporters comprise a family of functionally and pharmacologically diverse compound transporters with diverse effects. Therefore, the first question is, to which family of proteins does ABC belong, and secondly which particular member of the family has the same identical activities, functions and pharmacological of the ABC transporter of SEQ ID NO:9. The specification provides no clear answers. There is no disclosure of when a protein is considered sufficiently similar to be considered having all the properties of a family or of a specific species. There is no disclose in the specification of the percent

identity to related family members to assign functionality. Applicant has made sequence related predictions based on a limited homology between proteins, and based utility arguments on the family of proteins that have shown the closest identity. Based on the diversity of activity, functionality and ligand specificity of the ABC transporter family further experimentation is required to attach a specific function to the claimed ABC transporter. The specification does not disclose the specific function of the claimed ABC transporter, the transporter mechanism involved in movement of molecules across cell membranes, and the cytotoxic agents or ions that are moved. There is no disclosure by which claimed ABC transporter function, the utility in testing for its ability to confer drug resistance on cells expressing ABC (either normally or artificially), is based, or what specific drugs or ligands effect what specific transport, in cells expressing ABC, which in turn leads to utility in breeding. There is no disclosure of the scientific reasoning, that sequence similarity, in instant case, between claimed ABC transporter and other proteins that can be used to selectively predict a specific function, dysfunction, and activity of the ABC transporter family. Further the utility of claimed ABC, as postulated by applicant, consist of its potential role as an object of use testing.

Therefore the claimed ABC protein/DNA, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed polypeptide/DNA. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are useful to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of Auseful@ as it appears in 35 U.S.C. '101, which requires that an invention must have either an immediately apparent or fully disclosed real world utility. The court held that:

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a nucleic acid and protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the claimed protein/polynucleotide was, as of the filing date, useful for breeding of a microorganism for the purpose of modifying transport of amino acids across a cell membrane. Further it is not clear what use it would be to breed a microorganism for the purpose of modifying transport of amino acids across a cell membrane. Until some actual and specific significance can be attributed to the claimed ABC protein/DNA, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or a real world utility as of the filing date.

Also, for reasons set forth above and in the previous Office Action, Applicant has not presented sufficient evidence to support specific utility for the calimed DNA and protein. The present rejection under ' 101 follows Brenner v. Manson, as set forth above. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike Fujikawa v. Wattanasin, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under ' 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under ' 101. See, e.g., In re Swartz, 56 USPQ2d 1703 (Fed. Cir. 2000); In re Kirk, 153 USPQ 48 (CCPA 1967).

JANET ANDRES
PRIMARY EXAMINER